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## **Systemic interleukin-6 concentrations in patients with perimesencephalic non-aneurysmal subarachnoid hemorrhage**

Muroi, C ; Bellut, D ; Coluccia, D ; Mink, S ; Fujioka, M ; Keller, E

**Abstract:** Patients with spontaneous non-aneurysmal subarachnoid hemorrhage (non-aSAH) are considered to have a benign illness in contrast to patients with aSAH. The occurrence of the systemic inflammatory response syndrome has been linked to worse outcomes in patients with aSAH. We analyzed systemic interleukin (IL)-6, a proinflammatory cytokine, to determine whether its concentration differs between patients with non-aSAH and those with aSAH, reflecting the more benign illness. Daily systemic IL-6 levels were measured in the acute phase in 11 patients with non-aneurysmal perimesencephalic SAH (pmSAH), with bleeding strictly located around the midbrain, and in nine patients with non-aneurysmal non-perimesencephalic (non-pmSAH), with hemorrhage extending into adjacent cisterns (group 1). IL-6 levels were compared with those from patients suffering from aSAH with cerebral vasospasm (CVS) (group 2) and without CVS (group 3). The mean IL-6 level ( $\pm$ standard error of the mean) was significantly lower in group 1 compared to group 2 ( $9.9 \pm 1.9$  vs.  $29.1 \pm 6.7$  pg/mL,  $p=0.018$ ). The difference in mean IL-6 level between group 1 and 3 fell short of significance ( $9.9 \pm 1.9$  vs.  $14.9 \pm 1.1$  pg/mL,  $p=0.073$ ). Patients in group 1 had a significantly better outcome (Glasgow Outcome Scale score 4-5) compared to group 2 ( $p<0.001$ ) and a trend towards better outcome compared to group 3 ( $p=0.102$ ). A subgroup analysis revealed a higher mean IL-6 concentration in patients with non-pmSAH compared to patients with pmSAH ( $p=0.001$ ). We concluded that systemic IL-6 concentration reflects the severity of the inflammatory stress response and course of the illness. The more benign illness and good prognosis of patients with pmSAH or non-pmSAH in contrast to patients with aSAH is reflected by the lower concentrations of IL-6.

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# **Systemic Interleukin-6 Levels in Patients with Perimesencephalic Non-Aneurysmal Subarachnoid Hemorrhage**

Carl Muroi, MD<sup>1,2,3</sup>; David Bellut, MD<sup>3,4</sup>; Daniel Coluccia, MD<sup>2</sup>; Susanne Mink, MD<sup>1</sup>; Masayuki Fujioka, MD, PhD<sup>2,5</sup> and E. Keller, MD<sup>1</sup>

- 1 Neurocritical Care Unit, University Hospital Zurich, Switzerland
- 2 Department of Neurosurgery, Kantonsspital Aarau, Switzerland
- 3 Department of Neurosurgery, University Hospital Zurich, Switzerland
- 4 Institute of Neuroradiology, University Hospital Zurich, Switzerland
- 5 Department of Neurosurgery, Saiseikai Ibaraki Hospital, Osaka, Japan

## **Corresponding Author:**

Carl Muroi, MD

Neurochirurgische Klinik

Kantonsspital Aarau

CH-5001 Aarau

Switzerland

E-mail: carl.muroi@ksa.ch

Tel.: +41628385872

Fax.: +41628386629

## **Abstract**

Object: Patients with spontaneous non-aneurysmal subarachnoid hemorrhage (SAH) are considered to have a benign illness course in contrast to patients with aneurysmal (a)SAH. The occurrence of systemic inflammatory response syndrome has been linked to the worse outcome in patients with aSAH. We analyzed whether levels of systemic interleukin (IL)-6, a proinflammatory cytokine, differ in patients with non-aneurysmal SAH from those with aSAH, reflecting the more benign illness course.

Methods: Daily systemic IL-6 levels were measured in the acute phase in 11 patients with non-aneurysmal perimesencephal (pm)SAH, with bleeding strictly located around the midbrain, and in 9 patients with non-aneurysmal non-perimesencephalic (non-pm)SAH, with hemorrhage extending into adjacent cisterns (group 1). IL-6 levels were compared with those levels from patients suffering from aSAH with cerebral vasospasm (CVS) (group 2) and without CVS (group 3).

Results: The mean IL-6 level was statistically significantly lower in group 1 compared to group 2 ( $9.9 \pm 1.9$  vs.  $29.1 \pm 6.7$  pg/ml,  $p=0.018$ ). The difference of mean IL-6 level between group 1 and 3 fell short of significance ( $9.9 \pm 1.9$  vs.  $14.9 \pm 1.1$  pg/ml,  $p=0.073$ ). Patients in group 1 had a statistically significantly better outcome (GOS 4-5) compared to group 2 ( $p<0.001$ ) and a trend towards better outcome compared to group 3 ( $p=0.102$ ). A subgroup analysis revealed a significant higher mean IL-6 level ( $p=0.001$ ) in patients with non-pmSAH compared to patients with pm-SAH ( $p=0.012$ ).

Conclusions: Systemic IL-6 level reflects the severity of inflammatory stress response and illness course. The more benign illness course and good prognosis of patients with pmSAH or non-pmSAH in contrast to patients with aSAH is reflected by the lower IL-6 levels.

**Key words:** Interleukin-6, systemic inflammation, perimesencephalic subarachnoid hemorrhage, non-aneurysmal subarachnoid hemorrhage, cerebral vasospasm

## 1. Background

In a minority of patients with spontaneous subarachnoid hemorrhage (SAH) a bleeding source cannot be defined despite intensive radiological examinations.<sup>1,2</sup> Since the systematic description by van Gijn et al.,<sup>3</sup> perimesencephalic (pm)SAH and non-perimesencephalic (non-pm)SAH are commonly distinguished<sup>1,2,4</sup> In patients with pmSAH, the blood is located strictly around the midbrain and/or brainstem (Fig. 1A), while in patients with non-pmSAH the hemorrhage extends into adjacent cisterns (Fig. 1B).<sup>1,2</sup> The uncomplicated illness course and - particularly - the favorable outcome in patients with pmSAH are well-known facts. The risk of rebleeding and especially the risk of developing cerebral vasospasm (CVS) seem to be negligible.<sup>1,2,5,6</sup> In contrast, patients with non-pmSAH are reported to suffer from a higher risk of a complicated clinical course, development of CVS and subsequent worse outcome.<sup>1,4,6,7</sup> Inflammatory response with cytokine release is associated with severity of illness, clinical outcome and occurrence of CVS in patients with aSAH.<sup>8-10</sup> Higher levels of interleukin (IL)-6 in the cerebro-spinal fluid (CSF) have been linked to the occurrence of CVS and worse outcome.<sup>10-13</sup> Further, the occurrence of systemic inflammatory response syndrome has been linked to the development of CVS and worse outcome in patients with aSAH.<sup>14,15</sup> The possible significance of systemic leukocyte count has been discussed earlier.<sup>16,17</sup> Less has been reported on systemic IL-6 levels, however, increased levels were described.<sup>11,18,19</sup> Systemic IL-6 might originate from the central nervous system and/or reflect the systemic inflammatory response. The systemic IL-6 levels can be assumed to reflect the severity of illness and risk of CVS to a certain extent. In this study, we analyzed whether systemic IL-6 levels in patients with pmSAH and non-pmSAH differ from those with aSAH.

## 2. Methods

All patients with confirmed pmSAH and non-pmSAH, treated from 2007 to 2008, were included in this prospective observational study. The diagnosis of pmSAH and non-pmSAH were based on the initial CT scan and exclusion of a bleeding source by cerebral angiography: If the subarachnoid blood was strictly located in the interpeduncular and/or prepontine cistern, the patient was considered to suffer from pmSAH (Figure 1A). In these patients, no repeated angiography was performed. If the blood was extending to the adjacent cisterns, e.g. basal cisterns, the patient was considered to suffer from non-pmSAH (Figure 1B). In these patients, a repeated angiography was performed after the acute phase to definitely exclude a bleeding source. Patients with unknown bleeding date and late admission (>3 day after ictus) were excluded. A standardized treatment protocol in patients with SAH and the detailed assessment protocol for CVS were described elsewhere.<sup>20,21</sup> In brief, all patients received nimodipine 0.5 to 2 mg/h and high-dose magnesium-sulfate.<sup>22</sup> Daily transcranial Doppler (TCD) measurements were performed between day 4 and 14. In patients with suspected CVS (development of delayed ischemic neurological deficits, increased TCD blood flow velocities and/or perfusion deficits in perfusion CT scans), a modified triple-H therapy (hypertension with systolic blood pressure >150 mm Hg, normovolemia to minor hypervolemia, target hematocrit of 30%) was initiated. Cerebral angiography was performed if triple-H therapy was not effective. If CVS was angiographically confirmed (narrowing of the diameter of the vessel lumen >30%), balloon angioplasty and/or superselective papaverine instillation were performed. Patients with resistant or reoccurring CVS despite maximal aforementioned treatment were treated with barbiturate coma and/or hypothermia in terms of neuroprotection.<sup>23</sup> A follow-up CT scan was performed at least once before discharge from the neurocritical care unit. New ischemic lesions that could not be attributed to other causes were considered to be CVS-induced infarctions. Clinical and radiological assessment was carried out according to the World Federation of Neurosurgical Societies (WFNS). The outcome was assessed by the Glasgow outcome scale (GOS) 3 months after discharge. Systemic IL-6 levels and leukocyte (Lc) counts were measured daily until day 12 after ictus. IL-6 levels were measured by chemilumineszenz enzyme immunoassay (IMMULITE®

2500, Siemens, Germany) performed by the Institute for Clinical Chemistry, University Hospital of Zurich. Lc counts were performed by automated photometric measurement by the Division of Hematology, University Hospital of Zurich. The analyses were performed according to the laboratory standards and the internal quality control. The measurements were performed from blood samples taken in terms of clinical routine. Therefore, no additional blood samples were necessary for the current study. The study was approved by the local ethics committee. IL-6 levels, Lc counts and clinical outcome were compared between patients with pmSAH and non-pmSAH (group 1), patients with angiographically confirmed aSAH with CVS (group 2) and without CVS in the illness course (group 3). All patients were treated in the same time period.

Numeric variables are given as mean  $\pm$ SEM. Numeric variables between the 3 groups were compared by one-way ANOVA followed by the Bonferroni adjustment or - if no equal variance could be assumed - by the Tamhane's T2 post-hoc analysis. Binominal variables were analyzed by the chi-square test followed by a pair wise comparison with the Bonferroni adjustment. A p-value  $<0.05$  was assumed to be statistically significant.

### **3. Results:**

A pmSAH was identified in 11 patients and non-pmSAH in 9 patients (group 1). The control groups consisted of 99 patients presenting with aSAH. CVS did occur in 22 patients (22%) in the illness course (group 2), while the remaining 77 patients (78%) did not suffer from CVS (group 3). Patient characteristics are shown in Table 1. Group 1 had statistically significant more male patients than group 3 ( $p=0.009$ ). Patient groups did not differ concerning age. In group 1, a majority of 18 patients (90%) presented with clinically low grade hemorrhage (WFNS 1-3), while 12 (55%) and 22 (34%) patients presented with clinically high grade hemorrhage (WFNS 4-5) in group 2 and 3 respectively. The dichotomized severity grade was statistically significantly different between group 1 and 2 ( $p=0.006$ ), and a trend between group 1 and 3 could be observed ( $p=0.111$ ). The mean IL-6 level during the illness course was statistically significantly

lower in group 1 compared to group 2 ( $9.9 \pm 1.9$  vs.  $29.1 \pm 6.7$  pg/ml,  $p=0.018$ ). The difference of mean IL-6 level between group 1 and 3 fell short of significance ( $9.9 \pm 1.9$  vs.  $14.9 \pm 1.1$  pg/ml,  $p=0.073$ ). A trend towards higher mean IL-6 level was found in group 2 compared to group 3 ( $29.1 \pm 6.7$  vs.  $14.9 \pm 1.1$  pg/ml,  $p=0.103$ ). The results are shown as bar graphs in Figure 2A. The Lc counts during the illness course did not differ between the 3 groups (Figure 2B). Concerning outcome, patients in group 1 had a statistically significantly better outcome (GOS 4-5) compared to group 2 ( $p<0.001$ ) and a trend towards better outcome compared to group 3 ( $p=0.102$ ). Patients in group 2 had a statistically significantly worse outcome (GOS 1-3) compared to group 3 ( $p=0.018$ ). The results are summarized in Table 1. A subgroup analysis revealed a significant higher mean IL-6 level ( $14.7 \pm 3.2$  pg/ml vs.  $3.0 \pm 0.6$ ,  $p=0.001$ ) and a longer stay in the neurocritical care unit in patients with non-pmSAH compared to patients with pmSAH ( $16.4 \pm 2.1$  vs.  $10.2 \pm 1.1$  days,  $p=0.012$ ). In 2 of 9 patients with non-pmSAH, symptomatic CVS occurred in the illness course (Figure 1C and D). However, the outcome did not differ. Mean IL-6 level in patients with CVS compared to patients without CVS, regardless of the SAH pattern (i.e. aSAH, pmSAH or non-pmSAH), was statistically significantly higher ( $29.8 \pm 6.4$  pg/ml vs.  $13.8 \pm 0.9$  pg/ml,  $p=0.014$ ). Mean Lc counts of patients with CVS and without CVS, regardless of the SAH pattern, did not differ.

#### 4. Discussion

In the current study patients with pmSAH and non-pmSAH had a significantly lower mean IL-6 level during the illness course compared to patients with aSAH and symptomatic CVS. In comparison to patients with aSAH without CVS, a trend towards a lower level could be established. A trend towards higher mean IL-6 level was found in patients with CVS and without CVS in patients with aSAH. No differences concerning the mean Lc counts between the groups could be established. A subgroup analysis showed that patients with pmSAH had significantly lower mean IL-6 level compared to patients with non-pmSAH. Analysis, regardless of the SAH

pattern, showed a significantly higher mean IL-6 level in patients with CVS compared to patients without CVS.

The current results indicate that systemic IL-6 level reflects the severity of inflammatory stress response and illness course. Therefore, higher IL-6 levels might be predictive for poor outcome. As expected, the majority of patients with pmSAH or non-pmSAH presented with clinically “low-grade” SAH according to the WFNS grading, indicating a better neurological status at time of admission. The clinical outcome after 3 months in patients with pmSAH and non-pmSAH was better compared to patients with aSAH. However, with regard to IL-6, our results underline the obvious and already well-known fact that clinical severity at time of admission correlates with clinical outcome.<sup>24</sup> The demographic data of the current study revealed male dominance in patients with pmSAH or non-pmSAH in accordance with previously published data.<sup>1,6,7</sup> We could not show a tendency towards younger age in patients with pmSAH or non-pm SAH in contrast to previous reports.<sup>1</sup> The present significant difference in outcome between patients with and without CVS supports the common opinion that CVS remains a leading course of mortality and morbidity after aSAH. The occurrence of CVS in patients with pmSAH seems to be uncommon, while in patients with non-pmSAH the occurrence CVS has been more frequently described.<sup>4,7</sup> In the current study, symptomatic CVS did not occur in patients with pmSAH, while 2 out of 9 patients with non-pmSAH showed clinically relevant CVS. In the current patient population patients with non-pmSAH had a significantly longer stay in the neurocritical care unit, indicating a generally more complicated clinical course, which is in accordance with previous studies.<sup>1,2,7</sup> However, concerning the outcome, patients with pmSAH and non-pmSAH had a good overall outcome (GOS 4-5), without any statistical difference. There is an increasing evidence that inflammatory response with cytokines release is related to severity of illness, clinical outcome and occurrence of CVS in patients with SAH.<sup>8-10</sup> In particular high levels of IL-6, a pleiotropic proinflammatory cytokine, in the CSF have been linked with the occurrence of CVS and outcome.<sup>10-13</sup> Systemic IL-6 has been shown to be an independent predictor of outcome in unselected critically ill patients.<sup>25</sup> Less has been reported on systemic IL-6 levels in patients with aSAH. However, increased levels have been reported.<sup>11,18,19</sup> Systemic IL-6 might originate from



the central nervous system and/or reflect the systemic inflammatory response. Although the prognostic significance of systemic leukocytosis for the outcome of patients with SAH has been recognized earlier,<sup>16,17</sup> the positive relationship between systemic inflammatory response, occurrence of CVS and subsequent worse outcome is a newer observation.<sup>14,15</sup>

Taken abovementioned facts into account, systemic IL-6 levels might reflect the severity of illness and the risk of CVS development to a certain extent. The current study cannot answer the question if the systemic IL-6 has a direct impact on development of CVS or not. However, the results support the assertion that inflammation represents a common pathogenic pathway in the development of CVS or - at least - that systemic inflammatory response is a coherent epiphenomenon. To answer the question whether higher systemic IL-6 levels increase the risk of CVS after SAH requires further systemic clinical investigation.

In conclusion, the common assumption of the more benign illness course and good prognosis of patients with pmSAH or non-pmSAH in contrast to patients with aSAH is additionally supported by the lower IL-6 levels, whereas the higher IL-6 levels in patients with non-pmSAH support the common observation of a more complicated illness course with higher incidence of CVS compared to patients with pmSAH.

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## Figure Legends

Fig. 1. A) CT scan shows a pmSAH. The blood is located strictly around the midbrain and/or brainstem. B) CT scan showing a non-pmSAH. The hemorrhage extends into adjacent cisterns (arrows). C) Baseline angiography of a patient with non-pmSAH. D) A follow-up angiography shows apparent CVS of the middle cerebral artery and slight CVS of the anterior cerebral artery.

Fig. 2. Results shown as bar graphs. A) Systemic IL-6, \* statistically significant ( $p=0.018$ ), \*\* a trend was observed ( $p=0.073$ ), \*\*\* a trend was observed ( $p=0.103$ ). B) Systemic Lc counts, no significant differences between the groups.

**Table 1**  
Patient Characteristics and Results

	Group 1 (n=20)	Group 2 (n=22)	Group 3 (n=77)
Sex			
Female	7 (35%) <sup>a)</sup>	12 (55%)	55 (71%) <sup>a)</sup>
Male	13 (65%) <sup>a)</sup>	10 (45%)	22 (29%) <sup>a)</sup>
Age (mean ± SEM) [years]	56.6 ± 2.4	50.9 ± 2.5	56.9 ± 1.6
WFNS Grade			
1-3	18 (90%) <sup>b) c)</sup>	10 (45%) <sup>b)</sup>	51 (66%) <sup>c)</sup>
4-5	2 (10%) <sup>b) c)</sup>	12 (55%) <sup>b)</sup>	26 (34%) <sup>c)</sup>
IL-6 levels (mean ± SEM) [pg/ml]	9.9 ± 1.9 <sup>d) e)</sup>	29.1 ± 6.7 <sup>d) f)</sup>	14.9 ± 1.1 <sup>e) f)</sup>
Lc counts (mean ± SEM) [x1000/ul]	11.39 ± 0.38	11.70 ± 0.28	11.69 ± 0.14
GOS			
4-5	19 (95%) <sup>g) h)</sup>	9 (41%) <sup>g) j)</sup>	56 (73%) <sup>h) j)</sup>
1-3	1 (5%) <sup>g) h)</sup>	13 (59%) <sup>g) j)</sup>	21 (27%) <sup>h) j)</sup>

n: number of patients; SEM: standard error of the mean; WFNS: World Federation of Neurosurgical Societies; IL: interleukin; Lc: leukocytes; GOS: Glasgow outcome scale; a) statistically significant between group 1 and 3 ( $p=0.009$ ); b) statistically significant between group 1 and 2 ( $p=0.006$ ); c) a trend was observed between group 1 and 3 ( $p=0.111$ ); d) statistically significant between group 1 and 2 ( $p=0.018$ ); e) a trend was observed between group 1 and 3 ( $p=0.073$ ); f) a trend was observed between group 2 and 3 ( $p=0.103$ ); g) statistically significant between group 1 and 2 ( $p<0.001$ ); h) a trend was observed between group 1 and 3 ( $p=0.102$ ); j) statistically significant between group 2 and 3 ( $p=0.018$ ).

**Figure 1**  
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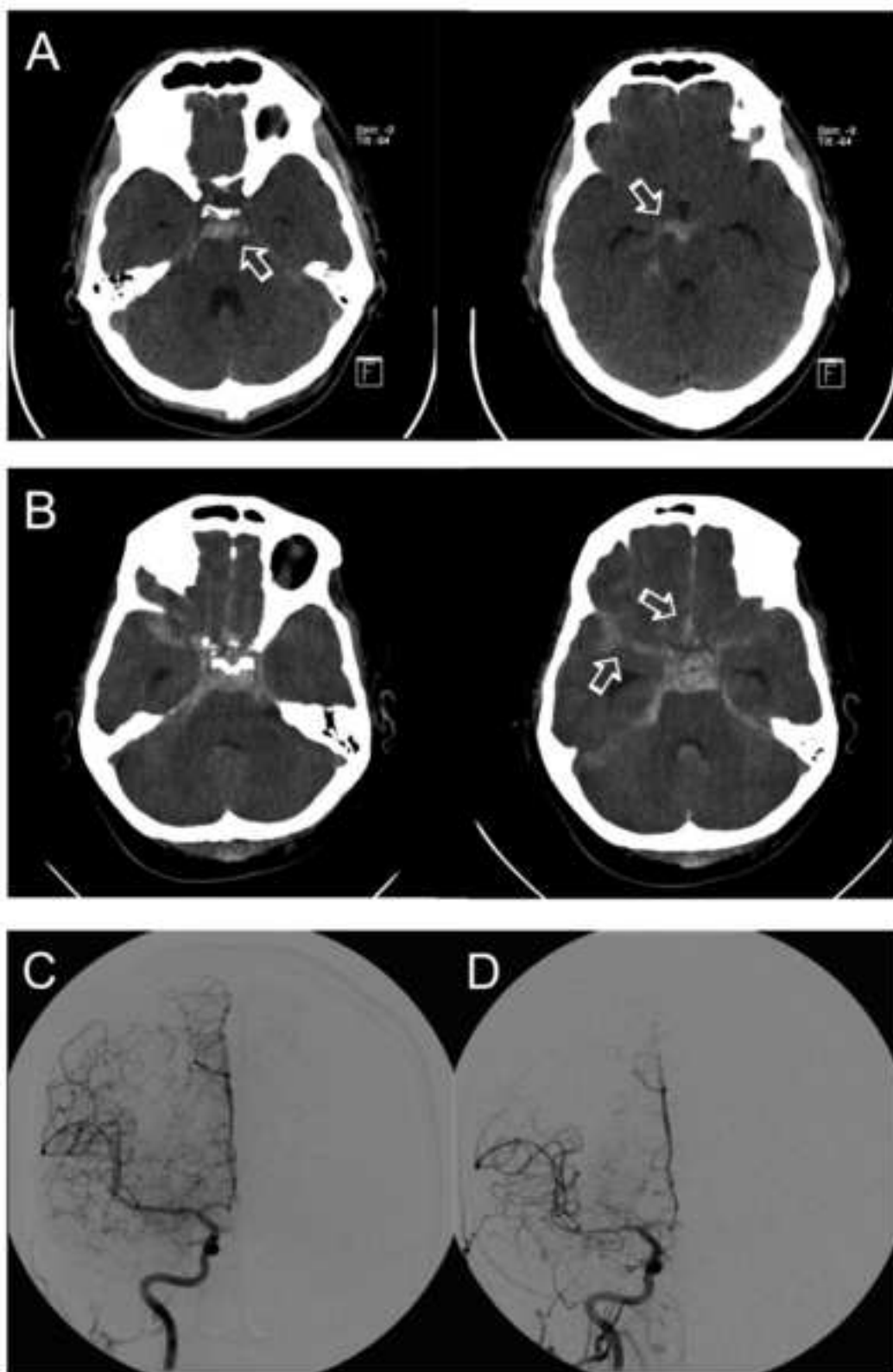


Figure 2  
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